(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 03/063820 A2

(51) International Patent Classification[7]: A61K 9/00

(21) International Application Number: PCT/EP03/00972

(22) International Filing Date: 31 January 2003 (31.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

170/2002	1 February 2002 (01.02.2002)	AT
192/2002	6 February 2002 (06.02.2002)	AT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/063820 A2

(54) Title: DEMIXING-STABLE GRANULATE

(57) Abstract: A process for the production of a granulate which is stable to segregation and which comprises granulate particles, which contain at least one β-lactama antibiotic and at least one β-lactamase inhibitor, useful for the production of pharmaceutical compositions.

Demixing-stable granulate

The present invention relates to pharmaceutical compositions.

Pharmaceutical compositions are frequently used in the form of powder mixtures or granulates, which are filled into single dose units such as plastic tubes, glass bottles, bags or sachets for administration. Powdered active ingredient, and optionally added excipient, e.g. which improve the taste or improve accessibility by machine, have to be formulated in such a way that exact dosage in a filling machine, i.e. an even distribution of active ingredient in each part of said composition should be guaranteed. If e.g. more than one active ingredient is used in a granulate for producing a pharmaceutical composition, active ingredient may be distributed unevenly over the different particle sizes of the granulate, e.g. one active ingredient may be found predominantly in the fine particles and another active ingredient in the coarse particles. This effect may lead to uneven dosage ratios in the single doses, e.g. if, when filling the granulate, pneumatic suction devices are used, which may cause an over-portional loss of fine grain portions in filled singles dose units. If such active ingredients are moist-granulated together, an even distribution of all active ingredients throughout the different grain sizes can be achieved, but e.g. because of the required moistening and drying steps and the large amounts of solvent needed, such process may be complex and in addition may be not appropriate for every active ingredient. In the case of active ingredients which are sensitive to moisture and/or heat labile, as is e.g. the case for the group of β-lactamase inhibitors, such a process might be useful to a limited extent only.
Dry compaction of active ingredients together with excipients, such as binders, may result in hard, densely compacted products, which, when used for administration in a liquid, such as a powder for oral suspension or dry syrup, may only dissolve slowly or may form a suspension only with difficulty. A sediment can even remain, which may have a negative effect on acceptance and patient compliance.

Now, surprisingly, we have found a process for the production of a granulate which is stable to segregation consisting of granulate particles comprising at least one β-lactam antibiotic and one β-lactamase inhibitor, and optionally at least one pharmaceutically acceptable excipients, in which both the β-lactam antibiotic and the β-lactamase inhibitor are distributed evenly over the different particle sizes of the granulate.

In one aspect, the present invention provides a process for the production of a granulate which is stable to segregation consisting of granulate particles comprising at least one β-lactam antibiotic and one β-lactamase inhibitor as active ingredients and optionally at least one pharmaceutically acceptable excipient, the process being characterised by the following steps:

a. preparing either

- excipient-free agglomerate particles with a bulk density of 0.1 to 1.5 g/cm^3 from said β-lactam antibiotic or from said β-lactamase inhibitor or from both, with a portion of less than 1% v/v of agglomerate particles having a diameter of 500 µm or greater than 500 µm,

or

- granulated particles with a bulk density of 0.1 to 1.5 g/ cm^3 from said β-lactam antibiotic or from said β-lactamase inhibitor or from both, with a portion of less than 1% v/v of granulated particles having a diameter of 500 µm or greater than 500 µm,

or

- hydrophobised granulated particles with a bulk density of 0.1 to 1.5 g/ cm^3 from said β-lactamase inhibitor with a portion of less than 1% v/v of hydrophobised granulated particles having a diameter of 500 µm or greater than 500 µm,

b. mixing either

- the excipient-free agglomerates or granulated particles or hydrophobised granulated particles from said β-lactamase inhibitor obtained in step a. with particles of said β-lactam antibiotic which are
  - in the form of excipient-free agglomerate particles obtained in step a., or
  - in the form of granulated particles obtained in step a., or
  - in the form of particles which are non-treated according to step a.,

  and optionally with at least one pharmaceutically acceptable excipient

or

- the excipient-free agglomerates or granulated particles from said β-lactam antibiotic obtained in step a. with particles from said β-lactamase inhibitor which are non-treated according to step a.,

  and optionally with at least one pharmaceutically acceptable excipient,

c. compressing the mixture obtained in step b. to obtain a pressing, and

d. breaking up the pressing obtained in step c, to obtain a granulate which is stable to segregation.

A granulate which is stable to segregation consisting of granulate particles comprising at least one β-lactam antibiotic and one β-lactamase inhibitor and optionally at least one pharmaceutically acceptable excipient produced according to a process of the present invention is hereinafter designated as "a granulate of (according to) the present invention."

Suitable β-lactam antibiotics are known e.g. from The Merck* Index, 12th Edition (1996) and include antibiotically active penicillins, cephalosporins, monobactams or carbapenems, including their pharmaceutically acceptable salts, solvates such as hydrates, preferably ampicillin e.g. in the form of a hydrate, such as a trihydrate (Merck* no. 628), amoxicillin e.g. in the form of a hydrate, such as a trihydrate (Merck* no. 617), penicillin V, e.g. in the form of a potassium salt (Merck* no. 7230), cephalexin, in the form of a hydrate, such as a monohydrate (Merck* no. 2021), Ticarcillin (Merck* no. 9568), Cefadroxil (Merck* no. 1963), more preferably ampicillin, amoxicillin, penicillin V, cephalexin.

Suitable β-lactamase inhibitors are β-lactamase inhibitors which, when combined with one or more of β-lactam antibiotics, e.g. such as indicated above, may result in improved *in vivo* activity of the β-lactam antibiotic, including their pharmaceutically acceptable salts, solvates and hydrates. Such β-lactamase inhibitors are known e.g. from The Merck* Index, 12th Edition (1996) and include clavulanic acid, e.g. in the form of a salt, such as a potassium salt (Merck* no. 2402), tazobactam, e.g. in the form of a salt, such as a sodium salt (Merck* no. 9251), and sulbactam, e.g. in the form of a salt, such as a sodium salt (Merck* no. 9058).

Combinations of β-lactam antibiotic and a β-lactamase inhibitor include, for example, amoxicillin (in the form of a trihydrate) and clavulanic acid, e.g. known under the Trade Mark name Augmentin® und ticarcillin and clavulanic acid, known under the Trade Mark name Timentin®.

A granulate of the present invention contains a β-lactam antibiotic and a β-lactamase inhibitor, preferably amoxicillin and clavulanic acid, e.g. in appropriate weight ratios, such as weight ratios of amoxicillin : clavulanic acid of 1:1 to 30:1, preferably 2:1 to 20:1, more preferably 2:1, 4:1, 5:1, 7:1, 8:1, 12:1, 14:1,16:1, 18:1 or 20:1.

A "granulate" as used herein, is understood to be a coagulation of agglomerates of powdered particles, wherein the particles are held together by electrostatic and/or van-der-Waals cohesive forces. "Granulated particles" as used herein are originating from a granulate, e.g. obtainable by breaking up a granulate. "Agglomerates", as used herein, are understood to be larger structures formed from particles in a liquid or gaseous environment, normally having an average equivalent diameter of 1 μm to 2000 μm. The cohesive forces between the particles inside an agglomerate are greater than the cohesive forces between two agglomerates or between agglomerate and powder particles inside a granulate. Agglomerates may, in general, be produced by a method as conventional, e.g. by compressing or by an agglomeration build-up process, or by conventional size enlargement processes, whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified. This can be done by e.g. dry methods, where no liquid is used for aggregation (compaction) or by wet methods, where liquid is utilized for agglomeration and followed by a drying process. A granulate (granulated material) may be unambigously distinguished, e.g. under a microscope such as an electron-microscope, from non-granulated material or agglomerates: whereas crystal-bridges representing the covalent bonds may be identified by microscopy in agglomerates (agglomerated material), such bridges cannot be found in a granulate

An excipient-free agglomerate of a β-lactam antibiotic or of a β-lactamase inhibitor, which is produced according to the process of the present invention in step a, contains a portion of less than 1% v/v, for example 0.0 % v/v to 0.9 % v/v, such as 0.0 % v/v to 0.5 % v/v, or 0.1 % v/v to 0.9 % v/v of agglomerate particles having a diameter of 500 μm or greater than 500 μm, optionally a diameter of equal or higher than 500 μm and lower than 3000 μm, having a bulk density of at least 0.1 g/cm^3, preferably at least 0.30 g/cm^3, more preferably 0.35 g/cm^3, such as 0.1 g/cm^3 to 1.5 g/cm^3, 0.3 g/cm^3 to 0.7 g/cm^3 or 0.4 g/cm^3 to 0.7 g/cm^3, most preferably 0.5 g/cm^3 to 0.7 g/cm^3. An excipient-free agglomerate as used herein is understood to contain no or no significant amounts, e.g. 0% to 5% w/w, preferably 0% o 2% w/w, more preferably 0% to 1% w/w, such as 0 to 0.1% w/w of excipient(s), such as excipient(s) as conventional, e.g. binders, disintegrants, etc. An excipient-free agglomerate may be produced by appropriate methods, e.g. by adding a solution or suspension of a β-lactam antibiotic or a β-lactamase inhibitor to a crystallizer fitted with a high shear stirrer and adding one or more anti-solvents, e.g. as described in WO00/41478 .

A granulate for the production of granulated particles produced according to step a. of the present invention may be obtained according to a method as described in WO 02/083129. In a preferred embodiment such granulate may be obtained by moist granulation, e.g. according to, e.g. analogously to, a moist granulation method as conventional, or, preferably, as described below:

As a starting material, a β-lactam antibiotic or a β-lactamase inhibitor, e.g. K-clavulanate, may be used in dry form or in solvent-moist form, preferably in solvent moist form, e.g. comprising an amount of 0 to 5% (w/w) of solvent, e.g. in a form as obtained from its preparation process, preferably in crystalline form. K-clavulanate is most preferably obtained from n-butanol or iso-butanol with or without water as a solvent from its preparation process, e.g. a preparation process as described in WO97/18216, the content of which and the content of literature cited therein is incorporated in the present invention by reference.

In moist granulation of a dry or solvent-moist β-lactam antibiotic or β-lactamase inhibitor, e.g. K-clavulanate, a granulation liquid may be used to obtain a granulation mass. A granulation liquid includes water or an organic solvent, or an organic solvent mixed with water, preferably water or an organic solvent mixed with water. In a granulation liquid an organic solvent is preferably an alcohol, including e.g. ethanol, n-butanol, isobutanol, preferably a mixture comprising n-butanol or isobutanol and containing 0.5 to 10% (v/v), e.g. 1.0 to 6% (v/v) of water.

A granulation mass appropriate for moist granulation may be obtained by mixing a granulation liquid with a β-lactam antibiotic or a β-lactamase inhibitor. The amount of granulating liquid is not critical and the minimum amount of granulating liquid may be easily determined. A granulation mass preferably contains a β-lactam antibiotic or a β-lactamase inhibitor, and granulating liquid in an amount of 5% (w/w based on wet mass), preferably of 6% (w/w) to 25% (w/w), preferably to 20% (w/w). In one embodiment the obtained granulation mass is dried and granulated β-lactam antibiotic or β-lactamase inhibitor is obtained. In another embodiment the granulation mass is extruded to obtain granulated β-lactam antibiotic or β-lactamase inhibitor. Preferably, the granulation mass is extruded, e.g. according, e.g. analogously, to conventional extruding methods, e.g. at appropriate extrusion temperatures, e.g. including temperatures from room temperature and below, e.g. 0°C to 10°C.

The obtained extruded mass is dried and granulated β-lactam antibiotic or β-lactamase inhibitor is obtained, or the extruded mass is passed through a sieve, preferably the extruded mass s passed through a sieve. A preferred mesh size of the sieve is in the range of 1.0 mm

to 4.0 mm, e.g. in the range of 2.0 mm to 3.0 mm. A sieved extruded mass obtained by such a method is dried to obtain granulated β-lactam antibiotic or β-lactamase inhibitor. Alternatively a (sieved) extruded mass may be (further) diminuished, e.g. according to, e.g. analogously, to a method as conventional, e.g. using a fast-action blade.

The granulation mass or the extruded mass, which is optionally sieved and/or further diminuished, undergoes a drying process. High temperatures may degrade, e.g. a β-lactamase inhibitor, e.g. clavulanic acid, and suitable drying conditions may be found by preliminary tests. Preferably a rapid pre-drying of the granulation mass or (sieved) extruded mass and gentle after-drying is carried out. Pre-drying may be effected by passing a gas, e.g. air, through the mass at temperatures in the range of room temperature and above, e.g. at temperatures of 25°C to 50°C, preferably 25°C to 40°C. Pre-drying preferably continues until the drying substrate has temperatures at or below room temperature, e.g. 25°C or less, for example 10°C to 25°C, preferably 15°C to 25°C. Drying may be carried out according to, e.g. analogously to, a method as conventional, e.g. by convection drying such as vacuum drying or dry-air drying. Suitable drying operations are effected as conventional such as by fluidized bed drying or by conveyor-belt-drying, e.g. in a shelf-dryer, a tray-dryer or a chamber-dryer. Pre-drying is preferably effected by belt drying or fluidised bed drying, more preferably fluidised bed drying. For after-drying, dry-air drying is preferably used.

Granulated β-lactam antibiotic or β-lactamase inhibitor is obtained upon drying. Granulated β-lactam antibiotic or β-lactamase inhibitor optionally may be broken up to obtain granulated K-clavulanate (particles) with a desired particle size, e.g. having a desired distribution of grain size, e.g. according, e.g. analogously, to a method as conventional, e.g. by use of a sieve, mill or a compacting device. A desired distribution of grain size may depend on a desired further processing. Preferably, no excipient is added during the whole process of moist-granulating in order to obtain excipient-free, granulated β-lactam antibiotic or β-lactamase inhibitor particles.

A β-lactam antibiotic or a β-lactamase inhibitor in the form of granulated particles may be prepared according to a process comprising the steps:

a. moistening a β-lactam antibiotic or a β-lactamase inhibitor with a granulating liquid to obtain a granulation mass,
b. optionally extruding the granulation mass obtained to form an extruded mass,
c. optionally passing, e.g. pressing, the extruded mass through a sieve,
d. drying the granulation mass or (sieved) extruded mass, and
e. diminuishing the size grain of of the granulate obtained.

Preferably, no excipient is added during said process.

Granulated β-lactam antibiotic or β-lactamase inhibitor, e.g. K-clavulanate may have advantageous processing properties, including high bulk densities, e.g. 0.1 to 1.5 g/ cm^3, preferably 0.5 to 0.8 g/ cm^3, such as 0.6 to 0.7 g/ cm^3, for example 0.61 to 0.7 g/cm^3.

"Hydrophobised granulated particles" as used herein are to be understood as granulated particles of a β-lactamase inhibitor, e.g. granulated clavulanate particles, which are protected from rapid dissolution in aqueous liquids at pH values that are different from those at the site of activity, with the result that degradation of the β-lactamase inhibitor, e.g. K-clavulanate, may be reduced or prevented in aqueous compositions. Such protection may be obtained by treating granulated particles with an oil and a hydrophobic solid, e.g. as described in WO 02/083129. In WO 02/083129 is described that such hydrophobised particles practically do not start to dissolve in aqueous liquid, e.g. if clavulanate particles are coated with an oil and a hydrophobic solid. Oils and hydrophobic solids used for hydrophibisation are e.g. as described in WO 02/083129, the content of which is introduced herein by reference.

An oil includes pharmaceutically acceptable oils, for example paraffin oils and silicone oils, preferably silicone oils, e.g. silicone oils which have antifoaming characteristics, e.g. siloxanes, such as dimethylpolysiloxane. The oil may be present as such or in a mixture with auxiliaries. Appropriate auxiliaries include e.g. flow-improving agents, e.g. silicon dioxides, e.g. highly dispersed SiO_2, such as Aerosil®. Hydrophobic solids include e.g. magnesium stearate. The ratio of amounts of a β-lactamase inhibitor to oil to hydrophobic solid is not critical. The minimum amount of oil and hydrophobic solid, which prevent dissolving, may be easily determined by preliminary tests. Conveniently 0.05 g to 0.3 g of oil and 0.05 g to 0.3 g of hydrophobic solid per gram of β-lactamase inhibitor may be appropriate.

Hydrophobised clavulanate may be produced by mixing clavulanate with an oil and a hydrophobic solid. A β-lactamase inhibitor, e.g. clavulanate, preferably K-clavulanate, may be used in a hydrophobisation process in a granulated particle form in which it is obtained by a production process, e.g. such as described above. Mixing may be effected in conventional mixers, e.g. by use of forced-flow mixers. Preferably, a β-lactamase inhibitor is pre-mixed with the oil, and the resulting mixture is mixed with the hydrophobic solid. A homogeneous mixture may be and should be obtained. Hydrophobised β-lactamase inhibitor namely granulated particles comprising a β-lactamase inhibitor together with an oil and a hydrophobic solid, e.g. particles coated with a (homogeneous) mixture of the oil and the hydrophobic solid, are obtained. β-Lactamase inhibitor particles should not stick together

under the mixing conditions and appropriate non-sticking-conditions may be easily determined, e.g. by preliminary testing.

It was found that hydrophobised β-lactamase inhibitor in the form of granulated particles, e.g. clavulanic acid or a salt thereof, may be stable in aqueous liquids, e.g water, aqueous suspensions, dispersions, salvia, i.e. clavulanate in hydrophobised clavulanate is practically not degraded in aqueous environment. However, hydrophobised β-lactamase inhibitor may be still well absorbed within the gastro-intestinal-tract in order to deliberate the β-lactamase inhibitor at its site of activity, i.e. the bacterial beta-lactamases. The advantageous processing properties of preferably excipient-free, granulated β-lactamase inhibitor may be maintained after hydrophobisation, e.g. if hydrophobisation is carried out under conditions in which the granulated, hydrophobised β-lactamase inhibitor particles do not stick together, granulated, hydrophobised β-lactamase inhibitor particles may maintain high abrasive resistance and high bulk density, e.g. 0.1 to 1.5 g/ cm^3, preferably 0.5 to 0.8 g/ cm^3, such as 0.6 to 0.7 g/cm^3.

The hydrophobised β-lactamase inhibitor particles obtained from such mixing process may be used to produce a granulate according to the present invention.

In another aspect, the present invention provides a process according to the present invention, in which process preparation of the excipient-free agglomerates in step a involves the following steps:

a21. mixing a solution or suspension of said β-lactamase inhibitor or of said β-lactam antibiotic in an appropriate liquid medium with one or more anti-solvents under stirring,

a22. isolating excipient-free agglomerates obtained in step a21., which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3, and

a23. drying the excipient-free agglomerates obtained in step a22.

Steps a21 to a23 may be carried out analogously to the methods disclosed in WO00/41478, e.g. they include appropriate

- liquid media in step a21, for example water, alcohols such as ethanol, methanol, 1-propanol, 2-butanol, 2-methylpropanol, ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone or esters, such as methyl acetate, ethyl acetate, butyl acetate, or a mixture of single indicated liquid media;

- anti-solvents in step a21, organic solvents in which the β-lactam antibiotic or the β-lactamase inhibitor is insoluble or only poorly soluble, e.g. ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, esters, such as methyl acetate, ethyl acetate, isobutyl acetate, alcohols such as 1-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, or a mixture of single indicated anti-solvents.

In the mixture consisting of liquid medium and anti-solvent, water should be present, for example in a portion of 0.05 to 10% v/v. The desired range of particle size of the excipient-free agglomerates may be influenced by agitating (stirring) conditions, e.g. by the rotational speed (and thus shear), tip velocity, power input of the agitator and by the choice and amount of anti-solvent added, and may be adjusted analogously to known methods, e.g. such as indicated in WO00/41478. The agitator may be e.g. a common turbine agitator, pitched blade agitator, toothed disks or rotor-stator mixer, e.g. with multiple stage mixing/shearing action, high shear mixer. The ratio between the diameter of the blades versus the diameter of the vessel should be between 0.2 to 0.9, preferably 0.2 to 0.5 depending on the type of agitator. The tip velocity may be in a range of 3 to 15 m/s. Excipient-free agglomerates obtained in in step a23 may be dried according to a method as conventional, e.g. by fluidised bed driers.

In another aspect, the present invention provides a process wherein production of the excipient-free agglomerates in step a. involves the following steps:

a11. preparing a mass suitable for extrusion consisting of a liquid and particles from said β-lactam antibiotic or from said β-lactamase inhibitor,

a12. extruding the mass obtained in step a11. with a twin-screw extruder, to obtain an extruded product,

a13. drying the extruded product obtained in step a12., and

a14. breaking up the dried extruded product of step a13. into excipient-free agglomerates, which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 μm or more than 500 μm and a bulk density of 0.1 to 1.5 g/cm^3.

Steps a11. to a13. may be carried out analogously to the process steps described in WO97/33564 the content of which is introduced herein by reference. In WO97/33564, it is described that a β-lactam compound can be kneaded with the assistance of a suitable liquid at 10°C to 80°C to a paste, which is extruded by a twin-screw extruder, after which the

extruded products obtained may be dried to produce agglomerates. Suitable liquids for step a11. includes liquid wherein the β-lactam antibiotic or the β-lactam inhibitor is insoluble or only begins to dissolve, e.g. water or organic solvents such as alcohols, e.g. ethanol, 2-propanol, 1-propanol or 1-butanol, or ketones, e.g. acetone. Drying according to step a13. may be carried out by use of drying apparatus as conventional, e.g. fluidised bed driers. In WO97/33564 it is disclosed that the excipient-free agglomerates of β-lactam antibiotics, which have the following distribution of grain size, are obtained:

< 100 µm: 1% to 30%

100 µm to 500 µm: 10% to 80%

500 µm to1000 µm: 10% to 80%

> 1000 µm: max. 30%

> 2000 µm: max. 0.5%.

A distribution of grain size of an excipient-free agglomerate with a portion of less than 1% by volume of agglomerate particles greater than 500 µm is not disclosed in WO97/33564.

Breaking up the dried agglomerates in step a14. may take place using appropriate methods, e.g. using a sieve with a mesh size of lower or equal 500 µm.

Excipient-free agglomerates of a β-lactam compound, which are appropriate for the production of a granulate that is stable to segregation according to the present invention have for example an average grain size, based on volume, of 30 µm, preferably 50 µm to 200 µm, preferably 180 µm, and the following distribution of grain size:

particle size fraction	**volume-based portion**
over 500µm	below 1%
200-500µm	5-30%
100-200µm	10-40%
below 100µm	30-80%

The bulk density of the excipient-free agglomerates produced according to step a. of the present invention is at least 0.1 g/cm^3, preferably 0.30 g/cm^3, more preferably 0.35 g/cm^3, such as 0.3 g/cm^3 to 0.7 g/cm^3 or 0.4 g/cm^3 to 0.7 g/cm^3, most preferably 0.5 g/cm^3 to 0.6 g/cm^3.

The bulk density of the granulated particles or the hydrophobised granulated particles produced in step a. of the present invention is at least 0.1 g/cm^3, preferably between 0.5 g/cm^3 and 0.8 g/cm^3.

The distribution of particle size of an agglomerate or granulate may be determined according to a method as conventional, e.g. by sieving or by a computing procedure (for which the conversion of the type of quantities (e.g. v/v or w/w) must be taken into consideration. If not otherwise indicated, the particle sizes indicated in the present application always refer to the type of quantity of the particle volume (v/v). The bulk density may be determined by a method as conventional, e.g. corresponding to DIN EN 543.

A granulate which is stable to segregation, and which can be produced according to the present invention, is understood to be a granulate in which all the pharmaceutical active ingredients, such as β-lactam antibiotics and β-lactamase inhibitors, are evenly distributed over all grain sizes, i.e. each individual active ingredient in each of the three following grain fractions

- above 80% percentile,
- between 80% percentile and 20% percentile, and
- below 20% percentile

deviates by a maximum of 7% w/w, preferably a maximum of 5% w/w, more preferably a maximum of 3% w/w such as from 0 to 7% w/w, from the portion of β-lactam antibiotics and β-lactamase inhibitors which is ideal for the respective grain fraction. The portion of active ingredient which is ideal for the respective grain fraction results from the quotient of the amount of active ingredient in the whole product and the volumetric or mass portion of the grain size fraction in the whole product. If e.g. a granulate exists with quantities of active ingredient totalling 1000 mg amoxicillin and 125 mg of clavulanic acid, then the portion of amoxicillin and clavulanic acid which is ideal for the grain fraction above the 80% percentile - a prerequisite is strict portionality of volume and mass of the granulate - is respectively 20% of the amount of active ingredient in the whole product, that is, 200 mg of amoxicillin and 25 mg of clavulanic acid. The grain fraction below 20% percentile represents the volume or the mass of the 20% smallest particles in the whole product, that above 80% percentile represents the volume or the mass of the 20% largest particles, the grain fraction between 20% percentile and 80% percentile represents the volume or mass of the remaining 60% of all particles in the whole product.

Step b. of the process of the present invention may be carried out as appropriate, e.g. using mixing apparatus, such as a freefall mixer. The second (or further) active ingredient compound may be admixed in powder form, e.g. in a particle size of 0.1 to 100 µm.

Excipients in step b. include conventional, pharmaceutically acceptable excipients, e.g. tabletting excipients, such as fillers, e.g. celluloses, such as Avicel®, binders such as polyvinyl pyrrolidones, e.g. Polyplasdone®, disintegrants such as modified starches, e.g. Starch 1500 J, Primojel®, cellulose derivatives, e.g. Ac-Di-Sol®, crosslinked polyvinyl pyrrolidones (PVP), flow-improving agents and lubricants, such as metal salts of stearic acid, e.g. magnesium stearate or talcum, sweetening agents such as sugar and sugar derivatives, such as saccharose, fructose, sorbitol, sweeteners, e.g. aspartame, saccharin, Acesulfam® K, thaumatin. Excipient(s) may be admixed before, during or after mixing in the second (or further) active ingredient(s), e.g. the β-lactam antibiotic or the β-lactamase inhibitor. The whole portion of excipient in the dry compressed tablets, which are obtained according to step c. of the process of the present invention, is preferably less than 100% by weight of the β-lactam antibiotic.

Compression of the mixture obtained in step b. into pressings or compressed tablets in step c. of the process of the present invention may be carried out using appropriate processes, e.g. with tabletting machines.

A granulate of the present invention or a granulate produced by a process of the present invention, preferably in association with pharmaceutically acceptable excipient(s), may provide a directly usable pharmaceutical composition.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, comprising adding further pharmaceutically acceptable excipient(s) to a granulate, e.g. admixing with, e.g. to a granulate which is obtained by a process according to the present invention.

Excipients which further may be added include e.g. flow-improving agents and lubricants, such as talcum, bentonite, desiccants, such as silicon dioxide, e.g. Aerosil®, fragrances in order to improve the taste or smell, such as fruit aromas, for example cherry, strawberry, raspberry or vanilla aromas.

A pharmaceutical composition of the present invention, includes for example

- a dispersible tablet, which is obtainable by compressing a granulate of the present invention,
- a suspension granulate, e.g. which is filled into suitable, single-dosable units, such as bags or sachets, vials, bottles, plastic tubes, and which may be reconstituted in appropriate liquid, e.g. aqueous liquid, to provide a pharmaceutical, e.g.oral, suspension.

In a further aspect, the present invention provides a process for the production of a pharmaceutical suspension, e.g. oral, comprising at least one β-lactam antibiotic and one β-lactamase inhibitor, comprising the steps

i. producing a granulate or a pharmaceutical composition of the present invention, and
ii. suspending said granulate or composition produced in step i. in aqueous liquid.

The aqueous liquid is a drinkable liquid, e.g. water. A pharmaceutical suspension of the present invention may be administered orally.

In a further aspect, the present invention provides a granulate which is stable to segregation and which contains granulate particles consisting of clavulanic acid and amoxicillin in a weight ratio of 1:3 to 1:30 and optionally excipient(s), which is characterised in that both, the clavulanic acid and the amoxicillin, are distributed in such a way that the respective portion thereof in each of the three following grain fractions

- above 80% percentile
- between 80% percentile and 20% percentile , and
- below 20% percentile

deviates by a maximum of 7% from the portion of corresponding clavulanic acid or amoxicillin which is suitable for the respective grain fraction in an ideal distribution.

In a further aspect, the present invention provides a pharmaceutical composition, e.g. a dispersible tablet or a(n) (oral) suspension granulate, comprising a granulate of the present invention, optionally together with excipient(s).

A granulate of the present invention, e.g. produced by a process of the present invention, may be used for the preparation of a medicament for treating bacterial infections.

It may enable simple handling and more precise dosaging during filling than in the case of known granulates or granulates produced by known methods, even if pneumatic suction devices are used. Such granulates/pharmaceutical compositions can be quickly and completely suspended in an aqueous solution to form a homogeneous suspension, which can have a beneficial effect on acceptance and compliance by patients.

In the following examples all temperatures are in degree Centigrade and are uncorrected.

In the TABLES, the following abbreviations are used:

- EX: example number
- T_M: casing temperature of the mixer in °C
- SOLV: granulation liquid, which is used for granulation to obtain the granulation mass
- %SOLV: amount of granulation liquid in %w/w of the total granulation mass. The percentages in parenthesis in the column %SOLV indicate the water portion in %v/v in the granulation liquid
- DRY: type of drying used
- DEGR: loss of K-clavulanate content, which is determined (HPLC) in % after granulation and drying, based on the K-clavulanate content before granulation and drying
- COL: coloration of K-clavulanate after granulation and drying, compared with the K-clavulanate before granulation and drying. "NO" in the column COL indicates none, "YES" indicates colouration
- T_Z: air inlet temperature in the fluidised bed drier in °C
- T_G: temperature of the dried substrate in the fluidised bed drier in °C
- SD: bulk density in g/ml

N.D.: not detected by method used (HPLC)

I. Examples for the production of K-clavulanate in granulated form

Process 1

K-clavulanate is mixed with the granulating liquid in a mixer with a cooled casing and the granulation mass obtained is dried.

Drying A)a): Dry air is passed through a container having a perforated bottom.

Drying A)b): Pre-drying in a fluidised bed drier at 30° or 40° air inlet temperature. When the dry substrate has reached a temperature of below 25°C, after-drying is effected by passing dry air through the container with a perforated bottom.

Upon drying K-clavulanate is obtained in granulated form. The granulate obtained is broken over a sieve of mesh size 1 mm.

In the TABLES, the following abbreviations are used:

- EX: example number
- T_M: casing temperature of the mixer in °C
- SOLV: granulation liquid, which is used for granulation to obtain the granulation mass
- %SOLV: amount of granulation liquid in %w/w of the total granulation mass. The percentages in parenthesis in the column %SOLV indicate the water portion in %v/v in the granulation liquid
- DRY: type of drying used
- DEGR: loss of K-clavulanate content, which is determined (HPLC) in % after granulation and drying, based on the K-clavulanate content before granulation and drying
- COL: coloration of K-clavulanate after granulation and drying, compared with the K-clavulanate before granulation and drying. "NO" in the column COL indicates none, "YES" indicates colouration
- T_Z: air inlet temperature in the fluidised bed drier in °C
- T_G: temperature of the dried substrate in the fluidised bed drier in °C
- SD: bulk density in g/ml

N.D.: not detected by method used (HPLC)

Results are as set out in TABLE 1 below:

TABLE 1

EX	T_M	SOLV	%SOLV	DRY	DEGR	COL
1	4	H_2O	7	A)a)	2.4	YES
2	4	EtOH (50%)	11	A)b)	1.3	NO
3	3	n-Butanol (4%)	20	A)b)	1.3	NO

EX	T_M	SOLV	%SOLV	DRY	DEGR	COL
4	3	n-Butanol (4%)	20	A)b)	0.6	NO

Process 2

K-clavulanate is mixed with n-butanol containing 4% water in a mixer having a cooled casing (3°C) and a granulation mass is obtained. The granulation mass is extruded through an extruder (screw extruder).

The extruded mass obtained is dried. Pre-drying is effected in a fluidised bed drier at 30° or 40° air inlet temperature T_Z until reaching a temperature T_G of the dried substrate, and after-drying is carried out by passing through dry air.

K-clavulanate is obtained in granulated form. No colouration of granulated K-clavulanate occurs compared with K-clavulanate before granulation and drying. The granulate obtained is broken over a sieve of mesh size 1.0 mm.

Results are as set out in TABLE 2 below:

TABLE 2

EX	%SOLV	T_Z	T_G	DEGR	SD
5	16	30	21	N.D.	0.57
6	17	40	26	N.D.	0.44
7	19	30	22	0.8	0.64

Process 3

K-clavulanate is mixed with n-butanol containing 4% water in a mixer having a cooled casing (2°), a granulation mass is obtained and extruded through an extruder (screw extruder). The extruded mass obtained is pressed through a sieve of mesh size 2 mm or 2.5 mm and the sieved extruded mass obtained is dried. Pre-drying is effected in a fluidised bed drier at 30° until reaching a temperature of the dried substrate of 22°, and after-drying is carried out by passing through dry air.

K-clavulanate is obtained in granulated form. No colouration of granulated K-clavulanate occurs compared with K-clavulanate before granulation and drying.

The granulate obtained is broken over a sieve having a mesh size of

a 0.8 mm

b 1.0 mm, or

c 1.5 mm.

K-clavulanate is obtained in granulated form with a bulk density in the case of

a. is of 0.63 g/ml

b. is of 0.64 g/ml, and

c. is of 0.67 g/ml.

II. Example for the production of K-clavulanate in granulated and hydrophobised form

148.6 g of K-clavulanate in granulated form, obtained according to a method of examples I, are mixed with 17.9 g of dimethylpolysiloxane and 17.9 g of magnesium stearate in a forced-flow mixer. Particles of K-clavulanate in granulated and hydrophobised form are obtained. Depending on the bulk density of K-clavulanate in granulated form used as a starting material the hydrophobised particles obtained have a granulate-corresponding bulk density of 0.5 to 0.8 g/ml.

The hydrophobised clavulanic acid particles are suspended in aqueous liquids (water). Degradation of clavulanic acid in the hydrophobised particles of that suspension was determined and it was found that practically no degradation of clavulanic acid occurred in that aqueous environment.

III a.) EXAMPLE for the production of a granulate which is stable to segregation, containing amoxicillin, potassium clavulanate (clavulanic acid in the form of a potassium salt) and excipients

A. Excipient-free amoxicillin agglomerate

Particles of amoxicillin in the form of a trihydrate moistened with acetone (10 to 15% by weight acetone based on the moist mass) are processed into an extrudable mass, which is extruded using a twin-screw extruder (screw length L/D = 3) at a throughput rate of 150 kg/h and at a maximum torque increase of the screws of 25% to 35%. The screws are equipped with conveyor elements, and right- and left-handed kneading blocks. An extruded product obtained is dried on a fluidised bed drier and broken up through a sieve of mesh size 500 µm. An excipient-free agglomerate of amoxicillin in the form of a trihydrate with the grain size distribution as set out in TABLE 3 is obtained.

TABLE 3

grain size fraction	volume-based grain size distribution
<100 µm	70%
100-500 µm	30%
>500 µm	0%

Bulk density: 0.6 g/cm^3

B. Granulate which is stable to segregation

A quantity of excipient-free agglomerates containing amoxicillin trihydrate, corresponding to 100 parts of amoxicillin, produced by the method in example III aA.), is mixed in a freefall mixer with powdered potassium clavulanate (clavulanic acid in the form of a potassium salt), in a quantity corresponding to 12.5 parts of clavulanic acid, and further with 20 parts of croscarmellose sodium, 1.2 parts of magnesium stearate, 45.3 parts of microcrystalline cellulose and 3 parts of sweetener (aspartame). A mixture obtained is pressed into pressings in a tabletting machine, and broken up over a sieve of mesh size of 1.2 mm. A granulate which is stable to segregation is obtained. The following TABLE 4 indicates the grain size distribution, the amounts of active ingredient for the individual grain size fractions in an ideal distribution ("ideal" column), the portions of active ingredient determined in the individual grain size fractions ("meas." column) and the percentage deviation of the values determined from those of the ideal values ("Dev." column). The deviation of the total amounts from the weighed amounts of active ingredient (e.g. 124.6 mg instead of 125 mg clavulanic acid and 980.4 mg instead of 1000 mg of amoxicillin) are believed to be attributed to inaccuracies or losses caused by the process.

TABLE 4

grain size fraction	distrib-ution	clavulanic acid (124.6 mg)			amoxicillin (980.4 mg)		
		meas [mg]	ideal [mg]	dev.	meas [mg]	ideal [mg]	dev.
>710 µm	28%	34.3	34.9	-1.69%	274.5	277.2	+0.98%
710-250 µm	24%	29.1	29.9	-2.69%	235.3	242.4	+3.02%
<250 µm	48%	61.2	59.8	+2.33%	470.6	460.8	-2.08%
total	100%	124.6	124.6	±0%	980.4	980.4	±0%

Example III b.) for comparison

Analogously to the method as described in example III a.) an excipient-free agglomerate is produced, with the difference that the extruded substrate in step A is not sieved. An excipient-free amoxicillin agglomerate is obtained with the grain size distribution as given in TABLE 5.

TABLE 5

grain size fraction	volume-based grain size distribution
<100 µm	31%
100-500 µm	48%
>500 µm	21%

After mixing with the components indicated under example III aB.) and producing compressed tablets which are subsequently dried and broken up on a sieve of mesh size of 2.1 mm, a granulate which is not stable to segregation is obtained. The properties of the granulate, such as grain size distribution and the established portions of active ingredients in the different grain size fractions, the amounts of active ingredient suitable for the individual grain size fractions in an ideal distribution ("ideal" column), the portions of active ingredient actually measured in the individual grain size fractions ("meas." column) and the percentage weight-based deviation of the values actually measured from the ideal values ("dev." column), are indicated in the following TABLE 6:

TABLE 6

grain size fraction	distrib-ution	clavulanic acid (122.1 mg)			amoxicillin (1005.5 mg)		
		meas [mg]	ideal [mg]	dev.	meas [mg]	ideal [mg]	dev.
>710 µm	25%	27.2	30.5	-10.95%	262.5	251.4	+4.43%
710-250 µm	43%	36.5	52.5	-30.41%	490.2	432.4	+13.38%
<250 µm	32%	58.4	39.1	+49.42%	252.8	321.8	-21.43%
Gesamt	100%	122.1	122.1	±0%	1005.5	1005.5	±0%

When comparing the values of TABLE 4 with those of TABLE 6, it is immediately evident that according to comparison example III b.) (granulate not produced according to the present invention) the two active ingredients amoxicillin and clavulanic acid are distributed unevenly over the different grain size fractions (more than 10% of weight based deviation), whereas in opposite to that according to example III a.) (production according to the present invention) the two active ingredients amoxicillin and clavulanic acid are distributed evenly over the different grain size fractions (weight based deviation less than 3%).

Example IV

1992 parts of a granulate produced according to example III a.), are mixed homogeneously with 80 parts of powder aroma of mixed fruit taste and 100 parts of amorphous silicon dioxide (Aerosil®). A pharmaceutically acceptable suspension granulate is obtained, which is filled by a filling machine into sachets each of 2.172 g, corresponding to a dosage per sachet of 1000 mg amoxicillin and 125 mg clavulanic acid with a total error tolerance of maximum ±5% w/w.

Patent Claims

1. A process for the production of a granulate which is stable to segregation consisting of granulate particles comprising at least one β-lactam antibiotic and one β-lactamase inhibitor as active ingredients and optionally pharmaceutically acceptable excipient, the process comprising the following steps:

   a. preparing either

   - excipient-free agglomerate particles with a bulk density of 0.1 to 1.5 g/cm^3 from said β-lactam antibiotic or from said β-lactamase inhibitor or from both, with a portion of less than 1% v/v of agglomerate particles having a diameter of 500 µm or greater than 500 µm,

   or

   - granulated particles with a bulk density of 0.1 to 1.5 g/ cm^3 from said β-lactam antibiotic or from said β-lactamase inhibitor or from both, with a portion of less than 1% v/v of granulated particles having a diameter of 500 µm or greater than 500 µm,

   or

   - hydrophobised granulated particles with a bulk density of 0.1 to 1.5 g/ cm^3 from said β-lactamase inhibitor with a portion of less than 1% v/v of hydrophobised granulated particles having a diameter of 500 µm or greater than 500 µm,

   b. mixing either

   - the excipient-free agglomerates or granulated particles or hydrophobised granulated particles from said β-lactamase inhibitor obtained in step a. with particles of said β-lactam antibiotic which are

   - in the form of excipient-free agglomerate particles obtained in step a., or

   - in the form of granulated particles obtained in step a., or

   - in the form of particles which are non-treated according to step a.,

   and optionally with at least one pharmaceutically acceptable excipient

   or

   - the excipient-free agglomerates or granulated particles from said β-lactam antibiotic obtained in step a. with particles from said β-lactamase inhibitor which are non-treated according to step a.,

   and optionally with at least one pharmaceutically acceptable excipient,

   c. compressing the mixture obtained in step b. to obtain a pressing, and

d. breaking up the pressing obtained in step c, to obtain a granulate which is stable to segregation.

2. A process according to claim 1 wherein the β-lactam antibiotic is amoxicillin and the β-lactamase inhibitor is clavulanic acid.

3. A process according to claims 2 wherein the weight ratio of clavulanic acid : amoxicillin is from 1:1 to 1:30.

4. A process according to any one of claims 1 to 3, wherein the preparation of the excipient-free agglomerates in step a comprises the following steps:

a11. preparing a mass suitable for extrusion consisting of a liquid and particles from said β-lactam antibiotic or from said β-lactamase inhibitor,

a12. extruding the mass obtained in step a11. with a twin-screw extruder, to obtain an extruded product,

a13. drying the extruded product obtained in step a12., and

a14. breaking up the dried extruded product of step a13. into excipient-free agglomerates, which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3.

5. A process according to any one of claims 1 to 3, wherein the production of the excipient-free agglomerates in step a comprises the following steps:

a21. mixing a solution or suspension of said β-lactamase inhibitor or of said β-lactam antibiotic in an appropriate liquid medium with one or more anti-solvents under stirring,

a22. isolating excipient-free agglomerates obtained in step a21., which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3, and

a23. drying the excipient-free agglomerates obtained in step a22.

6. A process for the production of a pharmaceutical composition, comprising mixing a granulate which is obtained according to any one of claims 1 to 5 with at least one pharmaceutically acceptable excipient.

7. A process according to claim 6 wherein the pharmaceutical composition is a dispersible tablet or a suspension granulate

8. A process for the production of a pharmaceutically applicable suspension comprising at least one β-lactam antibiotic and at least one β-lactamase inhibitor, which process comprises preparing a dispersible tablet or a suspension granulate as defined in claim 7 and suspending said dispersible tablet or a suspension granulate obtained in an aqueous medium.

9. A process according to any one of claims 1 to 8, wherein the β-lactam antibiotic is amoxicillin and the β-lactamase inhibitor is clavulanic acid, comprising the following steps:

i. preparing a mass suitable for extrusion consisting of acetone and particles of amoxicillin in the form of a trihydrate,

ii. extruding the mass obtained in step i. with a twin-screw extruder, to obtain an extruded product,

iii. drying the extruded product obtained in step ii.,

iv. breaking up the dried extruded product of step iii. To obtain excipient-free agglomerates, which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3,

v. mixing the excipient-free agglomerates obtained in step iv. with clavulanic acid in the form of a potassium salt and optionally excipients,

vi. compressing the mixture obtained in step v., to obtain a pressing, and

vii. breaking up the pressing obtained in step vi., to obtain a granulate which is stable to segregation.

10. A granulate which is stable to segregation consisting of granulate particles of clavulanic acid and amoxicillin in a weight ratio of 1:3 to 1:30 and optionally at least one pharmaceutically acceptable excipient, characterised in that both, the clavulanic acid and

the amoxicillin, are distributed such that the respective portion thereof in each of the three following grain fractions

- above 80% percentile
- between 80% percentile and 20% percentile, and
- below 20% percentile

of the granulate deviates by a maximum of 7% w/w of the respective grain fraction in an ideal distribution from the corresponding portion of clavulanic acid and amoxicillin.

11. A pharmaceutical composition comprising a granulate according to claim 10.

12. A pharmaceutical composition according to claim 11 which is a dispersible tablet or a suspension granulate.

13. Use of a granulate obtained from a process as defined in any one of claims 1 to 5 comprising at least one pharmaceutically acceptable excipient as a pharmaceutical composition.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 2003/063820 A3

(51) International Patent Classification[7]: A61K 9/00, 9/20, 9/50, 9/16

(21) International Application Number: PCT/EP2003/000972

(22) International Filing Date: 31 January 2003 (31.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

170/2002	1 February 2002 (01.02.2002)	AT
192/2002	6 February 2002 (06.02.2002)	AT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:
— *with international search report*

(88) Date of publication of the international search report:
15 January 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/063820 A3

(54) Title: DEMIXING-STABLE GRANULATE

(57) Abstract: A process for the production of a granulate which is stable to segregation and which comprises granulate particles, which contain at least one β-lactama antibiotic and at least one β-lactamase inhibitor, useful for the production of pharmaceutical compositions.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00972

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/20 A61K9/50 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 33564 A (RANEBURGER JOHANNES ;ZEISL ERICH (AT); BIOCHEMIE GMBH (AT)) 18 September 1997 (1997-09-18) page 5, line 5 -page 7, line 29 examples ---	1-4,6-8, 10-13
X	EP 1 142 574 A (SMITHKLINE BEECHAM SA ;SMITHKLINE BEECHAM BR LABORATO (FR); SMITHK) 10 October 2001 (2001-10-10) page 1, paragraph 7 -page 2, paragraph 13 page 4, paragraph 26 - paragraph 27 claims; examples ---	1-4,6-8, 10-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
2 July 2003	05/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Rankin, R

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00972

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 11261 A (GIST BROCADES BV ;GROENENDAAL JAN WILLEM (NL)) 11 March 1999 (1999-03-11) page 3, line 15 -page 4, line 17 page 4, line 20 -page 5, line 19 claims; examples	1-4,6-8, 10-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/00972

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 10-13
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 10-13

Present claim 1 relates to an extremely large number of possible processes. In fact, the claim contains so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the examples and the end product of the process of claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00972

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WO2003063820(A2,A3)[1].pdf
07/25/06 09:01 AM

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 03/063820 A2

(51) International Patent Classification[7]: A61K 9/00

(21) International Application Number: PCT/EP03/00972

(22) International Filing Date: 31 January 2003 (31.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

170/2002	1 February 2002 (01.02.2002)	AT
192/2002	6 February 2002 (06.02.2002)	AT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/063820 A2

(54) Title: DEMIXING-STABLE GRANULATE

(57) Abstract: A process for the production of a granulate which is stable to segregation and which comprises granulate particles, which contain at least one β-lactama antibiotic and at least one β-lactamase inhibitor, useful for the production of pharmaceutical compositions.

Demixing-stable granulate

The present invention relates to pharmaceutical compositions.

Pharmaceutical compositions are frequently used in the form of powder mixtures or granulates, which are filled into single dose units such as plastic tubes, glass bottles, bags or sachets for administration. Powdered active ingredient, and optionally added excipient, e.g. which improve the taste or improve accessibility by machine, have to be formulated in such a way that exact dosage in a filling machine, i.e. an even distribution of active ingredient in each part of said composition should be guaranteed. If e.g. more than one active ingredient is used in a granulate for producing a pharmaceutical composition, active ingredient may be distributed unevenly over the different particle sizes of the granulate, e.g. one active ingredient may be found predominantly in the fine particles and another active ingredient in the coarse particles. This effect may lead to uneven dosage ratios in the single doses, e.g. if, when filling the granulate, pneumatic suction devices are used, which may cause an over-portional loss of fine grain portions in filled singles dose units. If such active ingredients are moist-granulated together, an even distribution of all active ingredients throughout the different grain sizes can be achieved, but e.g. because of the required moistening and drying steps and the large amounts of solvent needed, such process may be complex and in addition may be not appropriate for every active ingredient. In the case of active ingredients which are sensitive to moisture and/or heat labile, as is e.g. the case for the group of β-lactamase inhibitors, such a process might be useful to a limited extent only.
Dry compaction of active ingredients together with excipients, such as binders, may result in hard, densely compacted products, which, when used for administration in a liquid, such as a powder for oral suspension or dry syrup, may only dissolve slowly or may form a suspension only with difficulty. A sediment can even remain, which may have a negative effect on acceptance and patient compliance.

Now, surprisingly, we have found a process for the production of a granulate which is stable to segregation consisting of granulate particles comprising at least one β-lactam antibiotic and one β-lactamase inhibitor, and optionally at least one pharmaceutically acceptable excipients, in which both the β-lactam antibiotic and the β-lactamase inhibitor are distributed evenly over the different particle sizes of the granulate.

In one aspect, the present invention provides a process for the production of a granulate which is stable to segregation consisting of granulate particles comprising at least one β-lactam antibiotic and one β-lactamase inhibitor as active ingredients and optionally at least one pharmaceutically acceptable excipient, the process being characterised by the following steps:

a. preparing either

- excipient-free agglomerate particles with a bulk density of 0.1 to 1.5 g/cm^3 from said β-lactam antibiotic or from said β-lactamase inhibitor or from both, with a portion of less than 1% v/v of agglomerate particles having a diameter of 500 µm or greater than 500 µm,

or

- granulated particles with a bulk density of 0.1 to 1.5 g/ cm^3 from said β-lactam antibiotic or from said β-lactamase inhibitor or from both, with a portion of less than 1% v/v of granulated particles having a diameter of 500 µm or greater than 500 µm,

or

- hydrophobised granulated particles with a bulk density of 0.1 to 1.5 g/ cm^3 from said β-lactamase inhibitor with a portion of less than 1% v/v of hydrophobised granulated particles having a diameter of 500 µm or greater than 500 µm,

b. mixing either

- the excipient-free agglomerates or granulated particles or hydrophobised granulated particles from said β-lactamase inhibitor obtained in step a. with particles of said β-lactam antibiotic which are
  - in the form of excipient-free agglomerate particles obtained in step a., or
  - in the form of granulated particles obtained in step a., or
  - in the form of particles which are non-treated according to step a.,

  and optionally with at least one pharmaceutically acceptable excipient

or

- the excipient-free agglomerates or granulated particles from said β-lactam antibiotic obtained in step a. with particles from said β-lactamase inhibitor which are non-treated according to step a.,

  and optionally with at least one pharmaceutically acceptable excipient,

c. compressing the mixture obtained in step b. to obtain a pressing, and

d. breaking up the pressing obtained in step c, to obtain a granulate which is stable to segregation.

A granulate which is stable to segregation consisting of granulate particles comprising at least one β-lactam antibiotic and one β-lactamase inhibitor and optionally at least one pharmaceutically acceptable excipient produced according to a process of the present invention is hereinafter designated as "a granulate of (according to) the present invention."

Suitable β-lactam antibiotics are known e.g. from The Merck* Index, 12th Edition (1996) and include antibiotically active penicillins, cephalosporins, monobactams or carbapenems, including their pharmaceutically acceptable salts, solvates such as hydrates, preferably ampicillin e.g. in the form of a hydrate, such as a trihydrate (Merck* no. 628), amoxicillin e.g. in the form of a hydrate, such as a trihydrate (Merck* no. 617), penicillin V, e.g. in the form of a potassium salt (Merck* no. 7230), cephalexin, in the form of a hydrate, such as a monohydrate (Merck* no. 2021), Ticarcillin (Merck* no. 9568), Cefadroxil (Merck* no. 1963), more preferably ampicillin, amoxicillin, penicillin V, cephalexin.

Suitable β-lactamase inhibitors are β-lactamase inhibitors which, when combined with one or more of β-lactam antibiotics, e.g. such as indicated above, may result in improved *in vivo* activity of the β-lactam antibiotic, including their pharmaceutically acceptable salts, solvates and hydrates. Such β-lactamase inhibitors are known e.g. from The Merck* Index, 12th Edition (1996) and include clavulanic acid, e.g. in the form of a salt, such as a potassium salt (Merck* no. 2402), tazobactam, e.g. in the form of a salt, such as a sodium salt (Merck* no. 9251), and sulbactam, e.g. in the form of a salt, such as a sodium salt (Merck* no. 9058).

Combinations of β-lactam antibiotic and a β-lactamase inhibitor include, for example, amoxicillin (in the form of a trihydrate) and clavulanic acid, e.g. known under the Trade Mark name Augmentin® und ticarcillin and clavulanic acid, known under the Trade Mark name Timentin®.

A granulate of the present invention contains a β-lactam antibiotic and a β-lactamase inhibitor, preferably amoxicillin and clavulanic acid, e.g. in appropriate weight ratios, such as weight ratios of amoxicillin : clavulanic acid of 1:1 to 30:1, preferably 2:1 to 20:1, more preferably 2:1, 4:1, 5:1, 7:1, 8:1, 12:1, 14:1,16:1, 18:1 or 20:1.

A "granulate" as used herein, is understood to be a coagulation of agglomerates of powdered particles, wherein the particles are held together by electrostatic and/or van-der-Waals cohesive forces. “Granulated particles” as used herein are originating from a granulate, e.g. obtainable by breaking up a granulate. "Agglomerates", as used herein, are understood to be larger structures formed from particles in a liquid or gaseous environment, normally having an average equivalent diameter of 1 μm to 2000 μm. The cohesive forces between the particles inside an agglomerate are greater than the cohesive forces between two agglomerates or between agglomerate and powder particles inside a granulate. Agglomerates may, in general, be produced by a method as conventional, e.g. by compressing or by an agglomeration build-up process, or by conventional size enlargement processes, whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified. This can be done by e.g. dry methods, where no liquid is used for aggregation (compaction) or by wet methods, where liquid is utilized for agglomeration and followed by a drying process. A granulate (granulated material) may be unambigously distinguished, e.g. under a microscope such as an electron-microscope, from non-granulated material or agglomerates: whereas crystal-bridges representing the covalent bonds may be identified by microscopy in agglomerates (agglomerated material), such bridges cannot be found in a granulate

An excipient-free agglomerate of a β-lactam antibiotic or of a β-lactamase inhibitor, which is produced according to the process of the present invention in step a, contains a portion of less than 1% v/v, for example 0.0 % v/v to 0.9 % v/v, such as 0.0 % v/v to 0.5 % v/v, or 0.1 % v/v to 0.9 % v/v of agglomerate particles having a diameter of 500 μm or greater than 500 μm, optionally a diameter of equal or higher than 500 μm and lower than 3000 μm, having a bulk density of at least 0.1 g/cm^3, preferably at least 0.30 g/cm^3, more preferably 0.35 g/cm^3, such as 0.1 g/cm^3 to 1.5 g/cm^3, 0.3 g/cm^3 to 0.7 g/cm^3 or 0.4 g/cm^3 to 0.7 g/cm^3, most preferably 0.5 g/cm^3 to 0.7 g/cm^3. An excipient-free agglomerate as used herein is understood to contain no or no significant amounts, e.g. 0% to 5% w/w, preferably 0% o 2% w/w, more preferably 0% to 1% w/w, such as 0 to 0.1% w/w of excipient(s), such as excipient(s) as conventional, e.g. binders, disintegrants, etc. An excipient-free agglomerate may be produced by appropriate methods, e.g. by adding a solution or suspension of a β-lactam antibiotic or a β-lactamase inhibitor to a crystallizer fitted with a high shear stirrer and adding one or more anti-solvents, e.g. as described in WO00/41478 .

A granulate for the production of granulated particles produced according to step a. of the present invention may be obtained according to a method as described in WO 02/083129. In a preferred embodiment such granulate may be obtained by moist granulation, e.g. according to, e.g. analogously to, a moist granulation method as conventional, or, preferably, as described below:

As a starting material, a β-lactam antibiotic or a β-lactamase inhibitor, e.g. K-clavulanate, may be used in dry form or in solvent-moist form, preferably in solvent moist form, e.g. comprising an amount of 0 to 5% (w/w) of solvent, e.g. in a form as obtained from its preparation process, preferably in crystalline form. K-clavulanate is most preferably obtained from n-butanol or iso-butanol with or without water as a solvent from its preparation process, e.g. a preparation process as described in WO97/18216, the content of which and the content of literature cited therein is incorporated in the present invention by reference.

In moist granulation of a dry or solvent-moist β-lactam antibiotic or β-lactamase inhibitor, e.g. K-clavulanate, a granulation liquid may be used to obtain a granulation mass. A granulation liquid includes water or an organic solvent, or an organic solvent mixed with water, preferably water or an organic solvent mixed with water. In a granulation liquid an organic solvent is preferably an alcohol, including e.g. ethanol, n-butanol, isobutanol, preferably a mixture comprising n-butanol or isobutanol and containing 0.5 to 10% (v/v), e.g. 1.0 to 6% (v/v) of water.

A granulation mass appropriate for moist granulation may be obtained by mixing a granulation liquid with a β-lactam antibiotic or a β-lactamase inhibitor. The amount of granulating liquid is not critical and the minimum amount of granulating liquid may be easily determined. A granulation mass preferably contains a β-lactam antibiotic or a β-lactamase inhibitor, and granulating liquid in an amount of 5% (w/w based on wet mass), preferably of 6% (w/w) to 25% (w/w), preferably to 20% (w/w). In one embodiment the obtained granulation mass is dried and granulated β-lactam antibiotic or β-lactamase inhibitor is obtained. In another embodiment the granulation mass is extruded to obtain granulated β-lactam antibiotic or β-lactamase inhibitor. Preferably, the granulation mass is extruded, e.g. according, e.g. analogously, to conventional extruding methods, e.g. at appropriate extrusion temperatures, e.g. including temperatures from room temperature and below, e.g. 0°C to 10°C.

The obtained extruded mass is dried and granulated β-lactam antibiotic or β-lactamase inhibitor is obtained, or the extruded mass is passed through a sieve, preferably the extruded mass s passed through a sieve. A preferred mesh size of the sieve is in the range of 1.0 mm

to 4.0 mm, e.g. in the range of 2.0 mm to 3.0 mm. A sieved extruded mass obtained by such a method is dried to obtain granulated β-lactam antibiotic or β-lactamase inhibitor. Alternatively a (sieved) extruded mass may be (further) diminuished, e.g. according to, e.g. analogously, to a method as conventional, e.g. using a fast-action blade.

The granulation mass or the extruded mass, which is optionally sieved and/or further diminuished, undergoes a drying process. High temperatures may degrade, e.g. a β-lactamase inhibitor, e.g. clavulanic acid, and suitable drying conditions may be found by preliminary tests. Preferably a rapid pre-drying of the granulation mass or (sieved) extruded mass and gentle after-drying is carried out. Pre-drying may be effected by passing a gas, e.g. air, through the mass at temperatures in the range of room temperature and above, e.g. at temperatures of 25°C to 50°C, preferably 25°C to 40°C. Pre-drying preferably continues until the drying substrate has temperatures at or below room temperature, e.g. 25°C or less, for example 10°C to 25°C, preferably 15°C to 25°C. Drying may be carried out according to, e.g. analogously to, a method as conventional, e.g. by convection drying such as vacuum drying or dry-air drying. Suitable drying operations are effected as conventional such as by fluidized bed drying or by conveyor-belt-drying, e.g. in a shelf-dryer, a tray-dryer or a chamber-dryer. Pre-drying is preferably effected by belt drying or fluidised bed drying, more preferably fluidised bed drying. For after-drying, dry-air drying is preferably used.

Granulated β-lactam antibiotic or β-lactamase inhibitor is obtained upon drying. Granulated β-lactam antibiotic or β-lactamase inhibitor optionally may be broken up to obtain granulated K-clavulanate (particles) with a desired particle size, e.g. having a desired distribution of grain size, e.g. according, e.g. analogously, to a method as conventional, e.g. by use of a sieve, mill or a compacting device. A desired distribution of grain size may depend on a desired further processing. Preferably, no excipient is added during the whole process of moist-granulating in order to obtain excipient-free, granulated β-lactam antibiotic or β-lactamase inhibitor particles.

A β-lactam antibiotic or a β-lactamase inhibitor in the form of granulated particles may be prepared according to a process comprising the steps:

a. moistening a β-lactam antibiotic or a β-lactamase inhibitor with a granulating liquid to obtain a granulation mass,
b. optionally extruding the granulation mass obtained to form an extruded mass,
c. optionally passing, e.g. pressing, the extruded mass through a sieve,
d. drying the granulation mass or (sieved) extruded mass, and
e. diminuishing the size grain of of the granulate obtained.

Preferably, no excipient is added during said process.

Granulated β-lactam antibiotic or β-lactamase inhibitor, e.g. K-clavulanate may have advantageous processing properties, including high bulk densities, e.g. 0.1 to 1.5 g/ cm^3, preferably 0.5 to 0.8 g/ cm^3, such as 0.6 to 0.7 g/ cm^3, for example 0.61 to 0.7 g/cm^3.

"Hydrophobised granulated particles" as used herein are to be understood as granulated particles of a β-lactamase inhibitor, e.g. granulated clavulanate particles, which are protected from rapid dissolution in aqueous liquids at pH values that are different from those at the site of activity, with the result that degradation of the β-lactamase inhibitor, e.g. K-clavulanate, may be reduced or prevented in aqueous compositions. Such protection may be obtained by treating granulated particles with an oil and a hydrophobic solid, e.g. as described in WO 02/083129. In WO 02/083129 is described that such hydrophobised particles practically do not start to dissolve in aqueous liquid, e.g. if clavulanate particles are coated with an oil and a hydrophobic solid. Oils and hydrophobic solids used for hydrophibisation are e.g. as described in WO 02/083129, the content of which is introduced herein by reference.

An oil includes pharmaceutically acceptable oils, for example paraffin oils and silicone oils, preferably silicone oils, e.g. silicone oils which have antifoaming characteristics, e.g. siloxanes, such as dimethylpolysiloxane. The oil may be present as such or in a mixture with auxiliaries. Appropriate auxiliaries include e.g. flow-improving agents, e.g. silicon dioxides, e.g. highly dispersed SiO_2, such as Aerosil®. Hydrophobic solids include e.g. magnesium stearate. The ratio of amounts of a β-lactamase inhibitor to oil to hydrophobic solid is not critical. The minimum amount of oil and hydrophobic solid, which prevent dissolving, may be easily determined by preliminary tests. Conveniently 0.05 g to 0.3 g of oil and 0.05 g to 0.3 g of hydrophobic solid per gram of β-lactamase inhibitor may be appropriate.

Hydrophobised clavulanate may be produced by mixing clavulanate with an oil and a hydrophobic solid. A β-lactamase inhibitor, e.g. clavulanate, preferably K-clavulanate, may be used in a hydrophobisation process in a granulated particle form in which it is obtained by a production process, e.g. such as described above. Mixing may be effected in conventional mixers, e.g. by use of forced-flow mixers. Preferably, a β-lactamase inhibitor is pre-mixed with the oil, and the resulting mixture is mixed with the hydrophobic solid. A homogeneous mixture may be and should be obtained. Hydrophobised β-lactamase inhibitor namely granulated particles comprising a β-lactamase inhibitor together with an oil and a hydrophobic solid, e.g. particles coated with a (homogeneous) mixture of the oil and the hydrophobic solid, are obtained. β-Lactamase inhibitor particles should not stick together

under the mixing conditions and appropriate non-sticking-conditions may be easily determined, e.g. by preliminary testing.

It was found that hydrophobised β-lactamase inhibitor in the form of granulated particles, e.g. clavulanic acid or a salt thereof, may be stable in aqueous liquids, e.g water, aqueous suspensions, dispersions, salvia, i.e. clavulanate in hydrophobised clavulanate is practically not degraded in aqueous environment. However, hydrophobised β-lactamase inhibitor may be still well absorbed within the gastro-intestinal-tract in order to deliberate the β-lactamase inhibitor at its site of activity, i.e. the bacterial beta-lactamases. The advantageous processing properties of preferably excipient-free, granulated β-lactamase inhibitor may be maintained after hydrophobisation, e.g. if hydrophobisation is carried out under conditions in which the granulated, hydrophobised β-lactamase inhibitor particles do not stick together, granulated, hydrophobised β-lactamase inhibitor particles may maintain high abrasive resistance and high bulk density, e.g. 0.1 to 1.5 g/ cm^3, preferably 0.5 to 0.8 g/ cm^3, such as 0.6 to 0.7 g/cm^3.

The hydrophobised β-lactamase inhibitor particles obtained from such mixing process may be used to produce a granulate according to the present invention.

In another aspect, the present invention provides a process according to the present invention, in which process preparation of the excipient-free agglomerates in step a involves the following steps:

a21. mixing a solution or suspension of said β-lactamase inhibitor or of said β-lactam antibiotic in an appropriate liquid medium with one or more anti-solvents under stirring,

a22. isolating excipient-free agglomerates obtained in step a21., which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3, and

a23. drying the excipient-free agglomerates obtained in step a22.

Steps a21 to a23 may be carried out analogously to the methods disclosed in WO00/41478, e.g. they include appropriate

- liquid media in step a21, for example water, alcohols such as ethanol, methanol, 1-propanol, 2-butanol, 2-methylpropanol, ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone or esters, such as methyl acetate, ethyl acetate, butyl acetate, or a mixture of single indicated liquid media;

- anti-solvents in step a21, organic solvents in which the β-lactam antibiotic or the β-lactamase inhibitor is insoluble or only poorly soluble, e.g. ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, esters, such as methyl acetate, ethyl acetate, isobutyl acetate, alcohols such as 1-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, or a mixture of single indicated anti-solvents.

In the mixture consisting of liquid medium and anti-solvent, water should be present, for example in a portion of 0.05 to 10% v/v. The desired range of particle size of the excipient-free agglomerates may be influenced by agitating (stirring) conditions, e.g. by the rotational speed (and thus shear), tip velocity, power input of the agitator and by the choice and amount of anti-solvent added, and may be adjusted analogously to known methods, e.g. such as indicated in WO00/41478. The agitator may be e.g. a common turbine agitator, pitched blade agitator, toothed disks or rotor-stator mixer, e.g. with multiple stage mixing/shearing action, high shear mixer. The ratio between the diameter of the blades versus the diameter of the vessel should be between 0.2 to 0.9, preferably 0.2 to 0.5 depending on the type of agitator. The tip velocity may be in a range of 3 to 15 m/s. Excipient-free agglomerates obtained in in step a23 may be dried according to a method as conventional, e.g. by fluidised bed driers.

In another aspect, the present invention provides a process wherein production of the excipient-free agglomerates in step a. involves the following steps:

a11. preparing a mass suitable for extrusion consisting of a liquid and particles from said β-lactam antibiotic or from said β-lactamase inhibitor,

a12. extruding the mass obtained in step a11. with a twin-screw extruder, to obtain an extruded product,

a13. drying the extruded product obtained in step a12., and

a14. breaking up the dried extruded product of step a13. into excipient-free agglomerates, which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3.

Steps a11. to a13. may be carried out analogously to the process steps described in WO97/33564 the content of which is introduced herein by reference. In WO97/33564, it is described that a β-lactam compound can be kneaded with the assistance of a suitable liquid at 10°C to 80°C to a paste, which is extruded by a twin-screw extruder, after which the

extruded products obtained may be dried to produce agglomerates. Suitable liquids for step a11. includes liquid wherein the β-lactam antibiotic or the β-lactam inhibitor is insoluble or only begins to dissolve, e.g. water or organic solvents such as alcohols, e.g. ethanol, 2-propanol, 1-propanol or 1-butanol, or ketones, e.g. acetone. Drying according to step a13. may be carried out by use of drying apparatus as conventional, e.g. fluidised bed driers. In WO97/33564 it is disclosed that the excipient-free agglomerates of β-lactam antibiotics, which have the following distribution of grain size, are obtained:

< 100 µm: 1% to 30%

100 µm to 500 µm: 10% to 80%

500 µm to1000 µm: 10% to 80%

> 1000 µm: max. 30%

> 2000 µm: max. 0.5%.

A distribution of grain size of an excipient-free agglomerate with a portion of less than 1% by volume of agglomerate particles greater than 500 µm is not disclosed in WO97/33564.

Breaking up the dried agglomerates in step a14. may take place using appropriate methods, e.g. using a sieve with a mesh size of lower or equal 500 µm.

Excipient-free agglomerates of a β-lactam compound, which are appropriate for the production of a granulate that is stable to segregation according to the present invention have for example an average grain size, based on volume, of 30 µm, preferably 50 µm to 200 µm, preferably 180 µm, and the following distribution of grain size:

particle size fraction	**volume-based portion**
over 500µm	below 1%
200-500µm	5-30%
100-200µm	10-40%
below 100µm	30-80%

The bulk density of the excipient-free agglomerates produced according to step a. of the present invention is at least 0.1 g/cm^3, preferably 0.30 g/cm^3, more preferably 0.35 g/cm^3, such as 0.3 g/cm^3 to 0.7 g/cm^3 or 0.4 g/cm^3 to 0.7 g/cm^3, most preferably 0.5 g/cm^3 to 0.6 g/cm^3.

The bulk density of the granulated particles or the hydrophobised granulated particles produced in step a. of the present invention is at least 0.1 g/cm^3, preferably between 0.5 g/cm^3 and 0.8 g/cm^3.

The distribution of particle size of an agglomerate or granulate may be determined according to a method as conventional, e.g. by sieving or by a computing procedure (for which the conversion of the type of quantities (e.g. v/v or w/w) must be taken into consideration. If not otherwise indicated, the particle sizes indicated in the present application always refer to the type of quantity of the particle volume (v/v). The bulk density may be determined by a method as conventional, e.g. corresponding to DIN EN 543.

A granulate which is stable to segregation, and which can be produced according to the present invention, is understood to be a granulate in which all the pharmaceutical active ingredients, such as β-lactam antibiotics and β-lactamase inhibitors, are evenly distributed over all grain sizes, i.e. each individual active ingredient in each of the three following grain fractions

- above 80% percentile,
- between 80% percentile and 20% percentile, and
- below 20% percentile

deviates by a maximum of 7% w/w, preferably a maximum of 5% w/w, more preferably a maximum of 3% w/w such as from 0 to 7% w/w, from the portion of β-lactam antibiotics and β-lactamase inhibitors which is ideal for the respective grain fraction. The portion of active ingredient which is ideal for the respective grain fraction results from the quotient of the amount of active ingredient in the whole product and the volumetric or mass portion of the grain size fraction in the whole product. If e.g. a granulate exists with quantities of active ingredient totalling 1000 mg amoxicillin and 125 mg of clavulanic acid, then the portion of amoxicillin and clavulanic acid which is ideal for the grain fraction above the 80% percentile - a prerequisite is strict portionality of volume and mass of the granulate - is respectively 20% of the amount of active ingredient in the whole product, that is, 200 mg of amoxicillin and 25 mg of clavulanic acid. The grain fraction below 20% percentile represents the volume or the mass of the 20% smallest particles in the whole product, that above 80% percentile represents the volume or the mass of the 20% largest particles, the grain fraction between 20% percentile and 80% percentile represents the volume or mass of the remaining 60% of all particles in the whole product.

Step b. of the process of the present invention may be carried out as appropriate, e.g. using mixing apparatus, such as a freefall mixer. The second (or further) active ingredient compound may be admixed in powder form, e.g. in a particle size of 0.1 to 100 μm.

Excipients in step b. include conventional, pharmaceutically acceptable excipients, e.g. tabletting excipients, such as fillers, e.g. celluloses, such as Avicel®, binders such as polyvinyl pyrrolidones, e.g. Polyplasdone®, disintegrants such as modified starches, e.g. Starch 1500 J, Primojel®, cellulose derivatives, e.g. Ac-Di-Sol®, crosslinked polyvinyl pyrrolidones (PVP), flow-improving agents and lubricants, such as metal salts of stearic acid, e.g. magnesium stearate or talcum, sweetening agents such as sugar and sugar derivatives, such as saccharose, fructose, sorbitol, sweeteners, e.g. aspartame, saccharin, Acesulfam® K, thaumatin. Excipient(s) may be admixed before, during or after mixing in the second (or further) active ingredient(s), e.g. the β-lactam antibiotic or the β-lactamase inhibitor. The whole portion of excipient in the dry compressed tablets, which are obtained according to step c. of the process of the present invention, is preferably less than 100% by weight of the β-lactam antibiotic.

Compression of the mixture obtained in step b. into pressings or compressed tablets in step c. of the process of the present invention may be carried out using appropriate processes, e.g. with tabletting machines.

A granulate of the present invention or a granulate produced by a process of the present invention, preferably in association with pharmaceutically acceptable excipient(s), may provide a directly usable pharmaceutical composition.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, comprising adding further pharmaceutically acceptable excipient(s) to a granulate, e.g. admixing with, e.g. to a granulate which is obtained by a process according to the present invention.

Excipients which further may be added include e.g. flow-improving agents and lubricants, such as talcum, bentonite, desiccants, such as silicon dioxide, e.g. Aerosil®, fragrances in order to improve the taste or smell, such as fruit aromas, for example cherry, strawberry, raspberry or vanilla aromas.

A pharmaceutical composition of the present invention, includes for example

- a dispersible tablet, which is obtainable by compressing a granulate of the present invention,
- a suspension granulate, e.g. which is filled into suitable, single-dosable units, such as bags or sachets, vials, bottles, plastic tubes, and which may be reconstituted in appropriate liquid, e.g. aqueous liquid, to provide a pharmaceutical, e.g.oral, suspension.

In a further aspect, the present invention provides a process for the production of a pharmaceutical suspension, e.g. oral, comprising at least one β-lactam antibiotic and one β-lactamase inhibitor, comprising the steps

i. producing a granulate or a pharmaceutical composition of the present invention, and
ii. suspending said granulate or composition produced in step i. in aqueous liquid.

The aqueous liquid is a drinkable liquid, e.g. water. A pharmaceutical suspension of the present invention may be administered orally.

In a further aspect, the present invention provides a granulate which is stable to segregation and which contains granulate particles consisting of clavulanic acid and amoxicillin in a weight ratio of 1:3 to 1:30 and optionally excipient(s), which is characterised in that both, the clavulanic acid and the amoxicillin, are distributed in such a way that the respective portion thereof in each of the three following grain fractions

- above 80% percentile
- between 80% percentile and 20% percentile , and
- below 20% percentile

deviates by a maximum of 7% from the portion of corresponding clavulanic acid or amoxicillin which is suitable for the respective grain fraction in an ideal distribution.

In a further aspect, the present invention provides a pharmaceutical composition, e.g. a dispersible tablet or a(n) (oral) suspension granulate, comprising a granulate of the present invention, optionally together with excipient(s).

A granulate of the present invention, e.g. produced by a process of the present invention, may be used for the preparation of a medicament for treating bacterial infections.

It may enable simple handling and more precise dosaging during filling than in the case of known granulates or granulates produced by known methods, even if pneumatic suction devices are used. Such granulates/pharmaceutical compositions can be quickly and completely suspended in an aqueous solution to form a homogeneous suspension, which can have a beneficial effect on acceptance and compliance by patients.

In the following examples all temperatures are in degree Centigrade and are uncorrected.

In the TABLES, the following abbreviations are used:

- EX: example number
- T_M: casing temperature of the mixer in °C
- SOLV: granulation liquid, which is used for granulation to obtain the granulation mass
- %SOLV: amount of granulation liquid in %w/w of the total granulation mass. The percentages in parenthesis in the column %SOLV indicate the water portion in %v/v in the granulation liquid
- DRY: type of drying used
- DEGR: loss of K-clavulanate content, which is determined (HPLC) in % after granulation and drying, based on the K-clavulanate content before granulation and drying
- COL: coloration of K-clavulanate after granulation and drying, compared with the K-clavulanate before granulation and drying. "NO" in the column COL indicates none, "YES" indicates colouration
- T_Z: air inlet temperature in the fluidised bed drier in °C
- T_G: temperature of the dried substrate in the fluidised bed drier in °C
- SD: bulk density in g/ml

N.D.: not detected by method used (HPLC)

I. Examples for the production of K-clavulanate in granulated form

Process 1

K-clavulanate is mixed with the granulating liquid in a mixer with a cooled casing and the granulation mass obtained is dried.

Drying A)a): Dry air is passed through a container having a perforated bottom.

Drying A)b): Pre-drying in a fluidised bed drier at 30° or 40° air inlet temperature. When the dry substrate has reached a temperature of below 25°C, after-drying is effected by passing dry air through the container with a perforated bottom.

Upon drying K-clavulanate is obtained in granulated form. The granulate obtained is broken over a sieve of mesh size 1 mm.

In the TABLES, the following abbreviations are used:

- EX: example number
- T_M: casing temperature of the mixer in °C
- SOLV: granulation liquid, which is used for granulation to obtain the granulation mass
- %SOLV: amount of granulation liquid in %w/w of the total granulation mass. The percentages in parenthesis in the column %SOLV indicate the water portion in %v/v in the granulation liquid
- DRY: type of drying used
- DEGR: loss of K-clavulanate content, which is determined (HPLC) in % after granulation and drying, based on the K-clavulanate content before granulation and drying
- COL: coloration of K-clavulanate after granulation and drying, compared with the K-clavulanate before granulation and drying. "NO" in the column COL indicates none, "YES" indicates colouration
- T_Z: air inlet temperature in the fluidised bed drier in °C
- T_G: temperature of the dried substrate in the fluidised bed drier in °C
- SD: bulk density in g/ml

N.D.: not detected by method used (HPLC)

Results are as set out in TABLE 1 below:

TABLE 1

EX	T_M	SOLV	%SOLV	DRY	DEGR	COL
1	4	H_2O	7	A)a)	2.4	YES
2	4	EtOH (50%)	11	A)b)	1.3	NO
3	3	n-Butanol (4%)	20	A)b)	1.3	NO

EX	T_M	SOLV	%SOLV	DRY	DEGR	COL
4	3	n-Butanol (4%)	20	A)b)	0.6	NO

Process 2

K-clavulanate is mixed with n-butanol containing 4% water in a mixer having a cooled casing (3°C) and a granulation mass is obtained. The granulation mass is extruded through an extruder (screw extruder).

The extruded mass obtained is dried. Pre-drying is effected in a fluidised bed drier at 30° or 40° air inlet temperature T_Z until reaching a temperature T_G of the dried substrate, and after-drying is carried out by passing through dry air.

K-clavulanate is obtained in granulated form. No colouration of granulated K-clavulanate occurs compared with K-clavulanate before granulation and drying. The granulate obtained is broken over a sieve of mesh size 1.0 mm.

Results are as set out in TABLE 2 below:

TABLE 2

EX	%SOLV	T_Z	T_G	DEGR	SD
5	16	30	21	N.D.	0.57
6	17	40	26	N.D.	0.44
7	19	30	22	0.8	0.64

Process 3

K-clavulanate is mixed with n-butanol containing 4% water in a mixer having a cooled casing (2°), a granulation mass is obtained and extruded through an extruder (screw extruder). The extruded mass obtained is pressed through a sieve of mesh size 2 mm or 2.5 mm and the sieved extruded mass obtained is dried. Pre-drying is effected in a fluidised bed drier at 30° until reaching a temperature of the dried substrate of 22°, and after-drying is carried out by passing through dry air.

K-clavulanate is obtained in granulated form. No colouration of granulated K-clavulanate occurs compared with K-clavulanate before granulation and drying.

The granulate obtained is broken over a sieve having a mesh size of

a 0.8 mm

b 1.0 mm, or

c 1.5 mm.

K-clavulanate is obtained in granulated form with a bulk density in the case of

a. is of 0.63 g/ml

b. is of 0.64 g/ml, and

c. is of 0.67 g/ml.

II. Example for the production of K-clavulanate in granulated and hydrophobised form

148.6 g of K-clavulanate in granulated form, obtained according to a method of examples I, are mixed with 17.9 g of dimethylpolysiloxane and 17.9 g of magnesium stearate in a forced-flow mixer. Particles of K-clavulanate in granulated and hydrophobised form are obtained. Depending on the bulk density of K-clavulanate in granulated form used as a starting material the hydrophobised particles obtained have a granulate-corresponding bulk density of 0.5 to 0.8 g/ml.

The hydrophobised clavulanic acid particles are suspended in aqueous liquids (water). Degradation of clavulanic acid in the hydrophobised particles of that suspension was determined and it was found that practically no degradation of clavulanic acid occurred in that aqueous environment.

III a.) EXAMPLE for the production of a granulate which is stable to segregation, containing amoxicillin, potassium clavulanate (clavulanic acid in the form of a potassium salt) and excipients

A. Excipient-free amoxicillin agglomerate

Particles of amoxicillin in the form of a trihydrate moistened with acetone (10 to 15% by weight acetone based on the moist mass) are processed into an extrudable mass, which is extruded using a twin-screw extruder (screw length L/D = 3) at a throughput rate of 150 kg/h and at a maximum torque increase of the screws of 25% to 35%. The screws are equipped with conveyor elements, and right- and left-handed kneading blocks. An extruded product obtained is dried on a fluidised bed drier and broken up through a sieve of mesh size 500 µm. An excipient-free agglomerate of amoxicillin in the form of a trihydrate with the grain size distribution as set out in TABLE 3 is obtained.

TABLE 3

grain size fraction	volume-based grain size distribution
<100 µm	70%
100-500 µm	30%
>500 µm	0%

Bulk density: 0.6 g/cm^3

B. Granulate which is stable to segregation

A quantity of excipient-free agglomerates containing amoxicillin trihydrate, corresponding to 100 parts of amoxicillin, produced by the method in example III aA.), is mixed in a freefall mixer with powdered potassium clavulanate (clavulanic acid in the form of a potassium salt), in a quantity corresponding to 12.5 parts of clavulanic acid, and further with 20 parts of croscarmellose sodium, 1.2 parts of magnesium stearate, 45.3 parts of microcrystalline cellulose and 3 parts of sweetener (aspartame). A mixture obtained is pressed into pressings in a tabletting machine, and broken up over a sieve of mesh size of 1.2 mm. A granulate which is stable to segregation is obtained. The following TABLE 4 indicates the grain size distribution, the amounts of active ingredient for the individual grain size fractions in an ideal distribution ("ideal" column), the portions of active ingredient determined in the individual grain size fractions ("meas." column) and the percentage deviation of the values determined from those of the ideal values ("Dev." column). The deviation of the total amounts from the weighed amounts of active ingredient (e.g. 124.6 mg instead of 125 mg clavulanic acid and 980.4 mg instead of 1000 mg of amoxicillin) are believed to be attributed to inaccuracies or losses caused by the process.

TABLE 4

grain size fraction	distrib-ution	clavulanic acid (124.6 mg)			amoxicillin (980.4 mg)		
		meas [mg]	ideal [mg]	dev.	meas [mg]	ideal [mg]	dev.
>710 µm	28%	34.3	34.9	-1.69%	274.5	277.2	+0.98%
710-250 µm	24%	29.1	29.9	-2.69%	235.3	242.4	+3.02%
<250 µm	48%	61.2	59.8	+2.33%	470.6	460.8	-2.08%
total	100%	124.6	124.6	±0%	980.4	980.4	±0%

Example III b.) for comparison

Analogously to the method as described in example III a.) an excipient-free agglomerate is produced, with the difference that the extruded substrate in step A is not sieved. An excipient-free amoxicillin agglomerate is obtained with the grain size distribution as given in TABLE 5.

TABLE 5

grain size fraction	volume-based grain size distribution
<100 µm	31%
100-500 µm	48%
>500 µm	21%

After mixing with the components indicated under example III aB.) and producing compressed tablets which are subsequently dried and broken up on a sieve of mesh size of 2.1 mm, a granulate which is not stable to segregation is obtained. The properties of the granulate, such as grain size distribution and the established portions of active ingredients in the different grain size fractions, the amounts of active ingredient suitable for the individual grain size fractions in an ideal distribution ("ideal" column), the portions of active ingredient actually measured in the individual grain size fractions ("meas." column) and the percentage weight-based deviation of the values actually measured from the ideal values ("dev." column), are indicated in the following TABLE 6:

TABLE 6

grain size fraction	distrib-ution	clavulanic acid (122.1 mg)			amoxicillin (1005.5 mg)		
		meas [mg]	ideal [mg]	dev.	meas [mg]	ideal [mg]	dev.
>710 µm	25%	27.2	30.5	-10.95%	262.5	251.4	+4.43%
710-250 µm	43%	36.5	52.5	-30.41%	490.2	432.4	+13.38%
<250 µm	32%	58.4	39.1	+49.42%	252.8	321.8	-21.43%
Gesamt	100%	122.1	122.1	±0%	1005.5	1005.5	±0%

When comparing the values of TABLE 4 with those of TABLE 6, it is immediately evident that according to comparison example III b.) (granulate not produced according to the present invention) the two active ingredients amoxicillin and clavulanic acid are distributed unevenly over the different grain size fractions (more than 10% of weight based deviation), whereas in opposite to that according to example III a.) (production according to the present invention) the two active ingredients amoxicillin and clavulanic acid are distributed evenly over the different grain size fractions (weight based deviation less than 3%).

Example IV

1992 parts of a granulate produced according to example III a.), are mixed homogeneously with 80 parts of powder aroma of mixed fruit taste and 100 parts of amorphous silicon dioxide (Aerosil®). A pharmaceutically acceptable suspension granulate is obtained, which is filled by a filling machine into sachets each of 2.172 g, corresponding to a dosage per sachet of 1000 mg amoxicillin and 125 mg clavulanic acid with a total error tolerance of maximum ±5% w/w.

Patent Claims

1. A process for the production of a granulate which is stable to segregation consisting of granulate particles comprising at least one β-lactam antibiotic and one β-lactamase inhibitor as active ingredients and optionally pharmaceutically acceptable excipient, the process comprising the following steps:

   a. preparing either

   - excipient-free agglomerate particles with a bulk density of 0.1 to 1.5 g/cm^3 from said β-lactam antibiotic or from said β-lactamase inhibitor or from both, with a portion of less than 1% v/v of agglomerate particles having a diameter of 500 µm or greater than 500 µm,

   or

   - granulated particles with a bulk density of 0.1 to 1.5 g/ cm^3 from said β-lactam antibiotic or from said β-lactamase inhibitor or from both, with a portion of less than 1% v/v of granulated particles having a diameter of 500 µm or greater than 500 µm,

   or

   - hydrophobised granulated particles with a bulk density of 0.1 to 1.5 g/ cm^3 from said β-lactamase inhibitor with a portion of less than 1% v/v of hydrophobised granulated particles having a diameter of 500 µm or greater than 500 µm,

   b. mixing either

   - the excipient-free agglomerates or granulated particles or hydrophobised granulated particles from said β-lactamase inhibitor obtained in step a. with particles of said β-lactam antibiotic which are

   - in the form of excipient-free agglomerate particles obtained in step a., or

   - in the form of granulated particles obtained in step a., or

   - in the form of particles which are non-treated according to step a.,

   and optionally with at least one pharmaceutically acceptable excipient

   or

   - the excipient-free agglomerates or granulated particles from said β-lactam antibiotic obtained in step a. with particles from said β-lactamase inhibitor which are non-treated according to step a.,

   and optionally with at least one pharmaceutically acceptable excipient,

   c. compressing the mixture obtained in step b. to obtain a pressing, and

d. breaking up the pressing obtained in step c, to obtain a granulate which is stable to segregation.

2. A process according to claim 1 wherein the β-lactam antibiotic is amoxicillin and the β-lactamase inhibitor is clavulanic acid.

3. A process according to claims 2 wherein the weight ratio of clavulanic acid : amoxicillin is from 1:1 to 1:30.

4. A process according to any one of claims 1 to 3, wherein the preparation of the excipient-free agglomerates in step a comprises the following steps:

a11. preparing a mass suitable for extrusion consisting of a liquid and particles from said β-lactam antibiotic or from said β-lactamase inhibitor,

a12. extruding the mass obtained in step a11. with a twin-screw extruder, to obtain an extruded product,

a13. drying the extruded product obtained in step a12., and

a14. breaking up the dried extruded product of step a13. into excipient-free agglomerates, which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3.

5. A process according to any one of claims 1 to 3, wherein the production of the excipient-free agglomerates in step a comprises the following steps:

a21. mixing a solution or suspension of said β-lactamase inhibitor or of said β-lactam antibiotic in an appropriate liquid medium with one or more anti-solvents under stirring,

a22. isolating excipient-free agglomerates obtained in step a21., which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3, and

a23. drying the excipient-free agglomerates obtained in step a22.

6. A process for the production of a pharmaceutical composition, comprising mixing a granulate which is obtained according to any one of claims 1 to 5 with at least one pharmaceutically acceptable excipient.

7. A process according to claim 6 wherein the pharmaceutical composition is a dispersible tablet or a suspension granulate

8. A process for the production of a pharmaceutically applicable suspension comprising at least one β-lactam antibiotic and at least one β-lactamase inhibitor, which process comprises preparing a dispersible tablet or a suspension granulate as defined in claim 7 and suspending said dispersible tablet or a suspension granulate obtained in an aqueous medium.

9. A process according to any one of claims 1 to 8, wherein the β-lactam antibiotic is amoxicillin and the β-lactamase inhibitor is clavulanic acid, comprising the following steps:

i. preparing a mass suitable for extrusion consisting of acetone and particles of amoxicillin in the form of a trihydrate,

ii. extruding the mass obtained in step i. with a twin-screw extruder, to obtain an extruded product,

iii. drying the extruded product obtained in step ii.,

iv. breaking up the dried extruded product of step iii. To obtain excipient-free agglomerates, which have a grain size portion of less than 1% by volume of the agglomerate particles with a particle diameter of 500 µm or more than 500 µm and a bulk density of 0.1 to 1.5 g/cm^3,

v. mixing the excipient-free agglomerates obtained in step iv. with clavulanic acid in the form of a potassium salt and optionally excipients,

vi. compressing the mixture obtained in step v., to obtain a pressing, and

vii. breaking up the pressing obtained in step vi., to obtain a granulate which is stable to segregation.

10. A granulate which is stable to segregation consisting of granulate particles of clavulanic acid and amoxicillin in a weight ratio of 1:3 to 1:30 and optionally at least one pharmaceutically acceptable excipient, characterised in that both, the clavulanic acid and

the amoxicillin, are distributed such that the respective portion thereof in each of the three following grain fractions

- above 80% percentile
- between 80% percentile and 20% percentile, and
- below 20% percentile

of the granulate deviates by a maximum of 7% w/w of the respective grain fraction in an ideal distribution from the corresponding portion of clavulanic acid and amoxicillin.

11. A pharmaceutical composition comprising a granulate according to claim 10.

12. A pharmaceutical composition according to claim 11 which is a dispersible tablet or a suspension granulate.

13. Use of a granulate obtained from a process as defined in any one of claims 1 to 5 comprising at least one pharmaceutically acceptable excipient as a pharmaceutical composition.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 2003/063820 A3

(51) International Patent Classification[7]: A61K 9/00, 9/20, 9/50, 9/16

(21) International Application Number: PCT/EP2003/000972

(22) International Filing Date: 31 January 2003 (31.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

170/2002	1 February 2002 (01.02.2002)	AT
192/2002	6 February 2002 (06.02.2002)	AT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:
— *with international search report*

(88) Date of publication of the international search report:
15 January 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/063820 A3

(54) Title: DEMIXING-STABLE GRANULATE

(57) Abstract: A process for the production of a granulate which is stable to segregation and which comprises granulate particles, which contain at least one β-lactama antibiotic and at least one β-lactamase inhibitor, useful for the production of pharmaceutical compositions.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00972

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/20 A61K9/50 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 33564 A (RANEBURGER JOHANNES ;ZEISL ERICH (AT); BIOCHEMIE GMBH (AT)) 18 September 1997 (1997-09-18) page 5, line 5 -page 7, line 29 examples ---	1-4,6-8, 10-13
X	EP 1 142 574 A (SMITHKLINE BEECHAM SA ;SMITHKLINE BEECHAM BR LABORATO (FR); SMITHK) 10 October 2001 (2001-10-10) page 1, paragraph 7 -page 2, paragraph 13 page 4, paragraph 26 - paragraph 27 claims; examples --- -/--	1-4,6-8, 10-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 July 2003	05/08/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Rankin, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00972

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 11261 A (GIST BROCADES BV ;GROENENDAAL JAN WILLEM (NL)) 11 March 1999 (1999-03-11) page 3, line 15 -page 4, line 17 page 4, line 20 -page 5, line 19 claims; examples ----	1-4,6-8, 10-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/00972

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 10-13
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 10-13

Present claim 1 relates to an extremely large number of possible processes. In fact, the claim contains so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the examples and the end product of the process of claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00972

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